Remarks

In accordance with present invention, there are provided chimeric proteins comprising a fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily (see Figure A schematic below).

Figure A – exemplary chimeric fusion protein construct

When these two protein units associate with each other or with another receptor member, a functional entity is formed, for example, a functional endodimer (single polypeptide chain of the chimeric fusion protein; see Figure B schematic below) or a functional heterodimer (two polypeptide chains – the chimeric fusion protein and another receptor polypeptide; see Figure C schematic below).

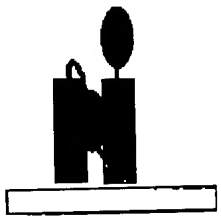

Figure B – exemplary endodimer

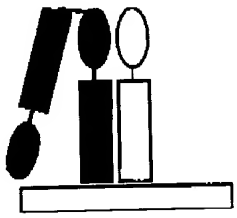

Figure C – exemplary heterodimer

Interestingly, many of the invention chimeric protein dimers display functional properties that are distinct from wild type dimers of members of the superfamily; for example, invention chimeric protein dimers display DNA binding superior to that of wild type complexes. Thus, the chimeric proteins of the invention can be used in a variety of methods to analyze and modulate gene expression in cells and organisms.

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Claims 1-11 and 13-60 were pending before this communication. Claims 23-51 and 55-60 have been withdrawn from consideration pursuant to the election of Group I with traverse. By this response, claim 1 has been amended to further define Applicants' invention with greater particularity, and claims 23-60 have been cancelled without prejudice. These amendments add no new matter as they are fully supported by the specification and the original claims. Attached hereto is a marked-up version of the changes made to the claims, labeled APPENDIX A.

Accordingly, claims 1-11, and 13-22 are currently under consideration. For the Examiner's convenience, a clean copy of these claims is also provided in APPENDIX B.

The rejection of claims 1-11, 13-22 and 52-54 under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to reasonably provide enablement for the chimeric proteins as claimed is respectfully traversed. It is respectfully submitted that the specification fully enables one of skill in the art to make and use the invention and is commensurate with the scope of the claims.

In fact, the Examiner has acknowledged that the specification is enabling for a chimeric protein "wherein the receptor is an ecdysone receptor, a Usp receptor or a retinoid X receptor" (see Office Action, Paper No. 12, at page 2, lines 15-16) based on the working examples of the present application. It is respectfully submitted that the working examples employ receptor members that are highly representative of the entire superfamily. Thus, additional examples with further superfamily members are clearly not necessary. Indeed, given the well characterized nature of all members of the nuclear receptor superfamily, additional examples with further superfamily members would merely be superfluous. Therefore, the claims should not be limited to just the working examples provided.

The present claims are directed to a chimeric protein comprising at least two functional protein units. Each of these functional protein units comprises at least the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily. The functional protein units form a functional entity, such that the resultant chimeric protein is biologically active.

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Applicants respectfully submit that the specification clearly enables one of skill in the art to make and use the chimeric proteins of the present invention commensurate in scope with the claims. All that is required is to make the chimeric protein comprising a fusion of at least two functional protein units (comprising the desired functional domains as claimed) using standard molecular biological techniques for making recombinant proteins, and to test whether the resulting protein exhibits one of the clearly identified biological functions using functional assays, such as those taught in the working examples of the specification.

The standard for determining enablement is whether the specification as filed provides sufficient information so as to permit one skilled in the art to make and use the claimed invention (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed" (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

According to this test of enablement, Applicants have provided more than a reasonable amount of guidance with respect to any experimentation required to carry out the present invention. With respect to the functional protein units, the specification teaches domains that can be used to form each functional protein unit and presents exemplary domains for use in the practice of the invention. For example, DNA binding domains are described at page 16, line 8, through page 18, line 13; ligand binding domains are described at page 14, line 26, through page 15, line 26; activation domains are described at page 18, line 14, through page 19, line 2; and dimerization domains are described at page 10, line 27, through page 11, line 18. One of skill in the art, in light of the teachings of the specification and knowledge in the art, could readily determine appropriate domains to assemble in the construction of a chimeric protein in order to achieve one or more biological functions. Moreover, Example 1 teaches the complete design and construction of exemplary chimeric fusion constructs.

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Furthermore, as previously noted in Applicants' response filed December 27, 2001 (Paper No. 11), members of the superfamily are commonly characterized by the presence of five domains, one of which is the required dimerization domain (see, for example, specification at page 11, lines 3-7); and significant homologies exist in domains within members of the superfamily, which have been extensively studied in the art. The receptors used in the examples provided (i.e., the ecdysone, Usp or retinoid X receptors) are highly representative of the superfamily. One of skill in the art would clearly appreciate the interchangeability of domains of different members of the superfamily to create novel functional chimeric proteins.

With respect to the resulting functional entity, for the reasons previously noted in Applicants' response filed December 27, 2001 (Paper No. 11), Applicants respectfully disagree with the Examiner's repeated efforts to unduly limit the functional properties which characterize the claimed chimeric proteins by requiring that a chimeric protein "respond to application of hormone" (see Office Action, Paper No. 12, at page 3, lines 2-4). Applicants further disagree with the Examiner's assertion that "insufficient direction is provided regarding the relationship of the chimeras structure and its function" (see Office Action, Paper No. 12, at page 3, lines 10-11).

The specification clearly defines a functional dimer or a functional entity as possessing at least some of the biological function of a dimer formed between two equivalent monomeric species (see, for example, specification at page 11, lines 26-30). "The biological function of such dimers includes one or more of the following properties: DNA binding, ligand binding, transactivation, and dimerization properties related to transactivation of a promoter operatively associated with a response element responsive to the invention chimeric protein" (see specification at page 12, lines 1-4). One of skill in the art, in light of the teachings of the specification and knowledge in the art, could readily determine whether a chimeric protein exhibited one or more of these biological functions. Moreover, Example 2 teaches an exemplary functional assay for transactivation activity of a chimeric fusion protein (see specification, at pages 57-61).

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Thus, one of skill in the art could readily identify putative functional domains to utilize in the preparation of such constructs to achieve a desired function (for example, incorporation of dimerization domains for dimerization function, ligand binding domains for ligand binding, etc.). Moreover, the type of experimentation required is merely routine, and could be readily conducted by one of skill in the art. As such, a considerable amount of experimentation is permissible, and the level of experimentation required to make and use the chimeric proteins of the present invention clearly does not amount to undue experimentation.

However, in order to reduce the issues and expedite prosecution, claim 1 has been amended to incorporate the explicit functions of the chimeric protein provided in the specification as noted above. This amendment is fully supported by the specification (see, for example, specification at page 12, lines 1-4).

For all of the reasons set forth above, it is respectfully submitted that the present claims as amended are fully enabled as required by 35 U.S.C. § 112, first paragraph. Moreover, it is respectfully submitted to be clear that those skilled in the art would not require undue experimentation to practice the claimed invention. Accordingly, reconsideration and withdrawal of the rejection of claims 1-11, 13-22 and 52-54 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

The rejection of claims 52-54 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make the invention is respectfully traversed. It is respectfully submitted that the specification fully enables one of skill in the art to make protein crystals comprising a purified chimeric protein.

However, in order to reduce the issues and expedite prosecution, claims 52-54 have been cancelled rendering this rejection of claims 52-54 moot. Accordingly, withdrawal of the rejection of claims 52-54 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

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The rejection of claims 1-11, 13-22 and 52-54 under 35 U.S.C. § 112, second paragraph, as allegedly being vague and indefinite in the recitation of the term "functional entity" is respectfully traversed. It is respectfully submitted that the claims are to be read in light of the specification and the subject term is clearly defined in the specification as filed.

Indeed, the Examiner's assertion that there is "no indication in the claim as to what function the protein must have" (see Office Action, Paper No. 12, at page 5, lines 19-20) is clearly in error. To the contrary, the metes and bounds of the claim can easily be determined in light of the teachings of the specification.

Specifically, the specification clearly defines a functional dimer or a functional entity as possessing at least some of the biological function of a dimer formed between two equivalent monomeric species (see, for example, specification at page 11, lines 26-30). "The biological function of such dimers includes one or more of the following properties: DNA binding, ligand binding, transactivation, and dimerization properties related to transactivation of a promoter operatively associated with a response element responsive to the invention chimeric protein" (see specification at page 12, lines 1-4). Therefore, the term functional entity is clear and definite in light of the specification.

However, in order to reduce the issues and expedite prosecution, claim 1 has been amended to include four types of functions contemplated for the chimeric proteins of the present invention. Accordingly, reconsideration and withdrawal of the rejection of claims 1-11, 13-22 and 52-54 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The rejection of claims 1-11 and 13-22 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,265,173 to Evans et al. (hereinafter referred to as "Evans") is respectfully traversed. The present claims require a chimeric protein comprising at least two functional protein units. Only Applicants describe a single polypeptide chain which itself is capable of dimerization to form a functional entity, for example as a functional endodimer (see Figure D comparison schematic below).

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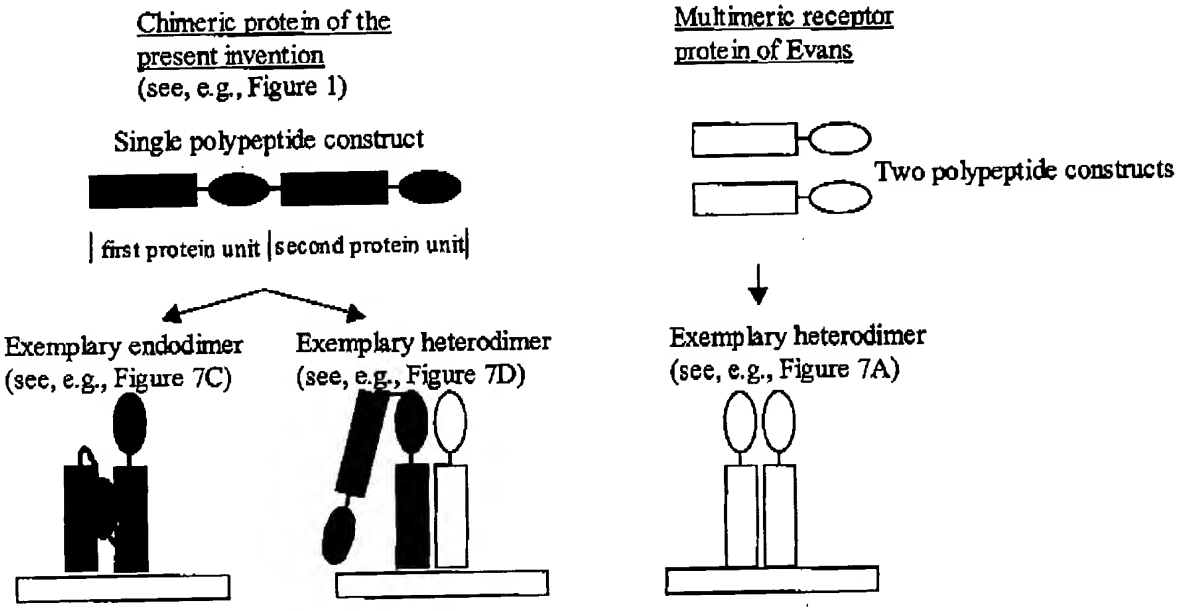

Figure D -- Comparison of the present invention to Evans

The chimeric proteins of the present invention are fusion proteins, which are defined in the specification as "a genetically engineered molecule in which two or more polypeptide units are fused into a single polypeptide molecule by the fusion of the open reading frames (ORFs) encoding the two or more separate protein units into a single ORF" (see specification at page 11, lines 19-22). Although the linker is optional, the two protein units are still part of the same single polypeptide chain, i.e., a single construct comprising a fusion of at least two protein units (see, for example, specification at Example 1, pages 57-60). In further efforts to clarify that the chimeric protein is a single polypeptide molecule, claim 1 has been amended to recite that the chimeric protein "is a fusion of" at least two functional protein units as claimed.

In contrast to the single polypeptide molecule contemplated by the present claims, Evans teaches multimeric receptor species, comprising at least one member of the steroid/thyroid superfamily of receptors and the ultraspiracle receptor, or a portion thereof (see, for example,

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Evans at column 3, lines 22-26). Although Evans represents a significant advance in the use of recombinant receptor dimers to regulate transactivation, Evans is directed to combinations of two receptor members, i.e., at least two distinct and separate polypeptides, such as heterodimeric (two molecules), heterotrimeric (three molecules) or heterotetrameric (four molecules) combinations (see, for example, Evans at column 3, lines 38-60).

The Examiner's erroneous assertion that Evans' "multimeric receptor could be an endodimer" (see Office Action, Paper No. 12, at page 7, line 1) indicates a misunderstanding of the different types of receptor constructs utilized in the present invention as compared to those of Evans. For example, endodimers contemplated by the present invention can only be formed from constructs disclosed herein, since endodimers, as defined in Applicants' specification, are single chain molecules that form an internal dimer to create a functional receptor dimer (see specification at page 12, lines 17-20). In contrast, all of Evans' multimeric receptor dimers are formed by at least two molecules as noted above, i.e. a receptor member and a Usp receptor, or portions thereof.

Therefore, only the present application teaches a chimeric receptor where two functional protein units are fused in a single polypeptide chain. Thus, Evans cannot anticipate the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-11 and 13-22 under 35 U.S.C. § 102(e).

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Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Appendices A and B

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APPENDIX A – ALTERED CLAIMS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 1 has been amended as follows:

1. (Amended) A chimeric protein comprising:

a fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily, and

an optional linker interposed therebetween,

wherein the at least two protein units form a functional entity**, such that said chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization**.

Claims 23-60 have been cancelled without prejudice.

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APPENDIX B – CLAIMS CURRENTLY UNDER CONSIDERATION

1. (Amended) A chimeric protein comprising:

a fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily, and

an optional linker interposed therebetween,

wherein the at least two protein units form a functional entity, such that said chimeric protein is capable of at least one function selected from the group consisting of DNA binding, ligand binding, transactivation and dimerization.

2. (Reiterated) The chimeric protein according to claim 1 wherein the entity is an endodimer.

3. (Reiterated) The chimeric protein according to claim 1 wherein each protein unit comprises a ligand binding domain, an optional hinge domain, and an optional DNA binding domain.

4. (Reiterated) The chimeric protein according to claim 3 wherein the functional entity is an endodimer.

5. (Reiterated) The chimeric protein according to claim 1 wherein at least one member is non-mammalian.

6. (Reiterated) The chimeric protein according to claim 5 wherein the at least one member is from an insect species.

7. (Reiterated) The chimeric protein according to claim 1 wherein at least one functional protein unit comprises the dimerization domain of an ecdysone receptor.

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8. (Reiterated) The chimeric protein according to claim 7 wherein the ecdysone receptor comprises the dimerization domain of a *Drosophila* ecdysone receptor.

9. (Reiterated) The chimeric protein according to claim 7 wherein the ecdysone receptor comprises the dimerization domain of a Lepidoptera ecdysone receptor.

10. (Reiterated) The chimeric protein according to claim 7 wherein the ecdysone receptor comprises the dimerization domain of a *Bombyx* ecdysone receptor.

11. (Reiterated) The chimeric protein according to claim 5 wherein at least one functional protein unit comprises the dimerization domain of the *ultraspiracle* protein.

13. (Reiterated) The chimeric protein according to claim 1 wherein at least one functional protein unit comprises the dimerization domain of the retinoid X receptor.

14. (Reiterated) The chimeric protein according to claim 1 wherein the protein units are independently selected from the group consisting of glucocorticoid receptors, mineralocorticoid receptors, estrogen receptors, progesterone receptors, androgen receptors, Vitamin D3 receptors, retinoic acid receptors, retinoid X receptors, peroxisome proliferator-activated receptors, thyroid hormone receptors, and steroid and xenobiotic receptors, farnesoid X receptor, pregnenolone X receptor, liver X receptor, and BXR.

15. (Reiterated) The chimeric protein according to claim 1 wherein the linker contains from about 5 to about 245 amino acids.

16. (Reiterated) The chimeric protein according to claim 15 wherein the linker contains from about 53 to about 125 amino acids.

17. (Reiterated) The chimeric protein according to claim 15 wherein the linker comprises glycine, proline, serine, alanine and threonine residues.

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18. (Previously amended) The chimeric protein according to claim 15 wherein the linker comprises the amino acid sequence of SEQ ID NO:15.

19. (Reiterated) The chimeric protein according to claim 3 wherein one or more protein units further comprise a C-terminal domain.

20. (Reiterated) The chimeric protein according to claim 3 wherein the DNA binding domains of one or more protein units comprise 66 to 68 amino acids, including 9 cysteines.

21. (Reiterated) The chimeric protein according to claim 3 wherein the hinge domain of one or more protein units is the *Bombyx* hinge domain.

22. (Reiterated) The chimeric protein according to claim 1 wherein one or more protein units further comprise an activation domain.

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